REMARKS

Preliminary Amendment

Applicants have amended the claims to more particularly claim the present invention. Support for the amendments to or new Claims 2, 16, 40, 41, 62 and 66 is found in the specification on page 7, lines 31-32. Support for the amendments to Claims 38 and 44 is found in the specification on page 3, lines 9-12 and page 8, lines 13-18. Support for new Claims 63-65 is found in the specification on page 7, lines 29-34 and page 16, lines 16, 22, 26, 29, 35; and page 17, lines 5-10.

Response to Restriction Requirement

The Examiner has restricted the claims into two groups as follows: Group I (Claims 1-10, 12, 14-33 and 37-61); and Group II (Claims 34-36).

Applicants provisionally elect to prosecute the claims of Group I, without traverse. With regard to Group II, Applicants acknowledge the right to amend the claims of Group II to be commensurate in scope with the claims of Group I with the goal of ultimately requesting rejoinder of such method claims with allowable product claims of Group I. In re Brouwer, 37 USPQ2d 1663 (Fed. Cir. 1996); In re Ochiai, 37 USPQ2d 1127 (Fed. Cir. 1995).

The Examiner has also required a species election among various specific proteins in Group I. Applicants elect, with traverse, to prosecute species (32), directed to erythropoietin (EPO). Applicants submit that Claims 1-7, 15, 16, 19-20, 22-38, 40-46, 52, 53, 57-66 read on the elected species, with Claims 1-7, 15, 24, 26-34, 37, 42-43, 45-46, 52, and 62-65 being generic.

Applicants traverse the Examiner's contention that the species of Group I do not relate to a single general inventive concept under PCT Rule 13.1 or 13.2. The Examiner contends that the species lack the same or corresponding special technical feature because each species of the fusion protein represents a structurally and functionally different chemical compound which lack a common utility based upon a common structural feature that identifies the basis for the common utility. To the contrary, the fusion proteins of the present invention are linked by the common special technical feature of being Ig fusion proteins in which a soluble protein in which a growth factor or cytokine (and specifically, members of the growth hormone supergene family) is joined to an Ig domain *in a specific manner* that results in a fusion protein that effectively preserves the biological activity of

the natural soluble protein as compared to any previously described fusion protein using these types of soluble proteins. First, the Ig domains specified in the present claims share the common technical feature of the absence of a variable region, so that the resulting fusion proteins will not be directed to *in vivo* sites due to immunoglobulin binding. Instead, the activity and *in vivo* targeting of the fusion protein results from the growth factor or cytokine portion. Second, the soluble protein is joined either directly to an Ig domain without an intervening peptide linker, or in a specific orientation (by its carboxy-terminus to the amino-terminus of the Ig domain) by a *specific* amino acid linker. The specific amino acid linker, when one is used, has a very specific sequence in that it may only consist of a mixture of two or more of four particular amino acid residues. In all cases, the joining of the soluble protein to the Ig domain in this manner results in a fusion protein with significant biological activity as compared to the native protein. Such proteins have the advantage of being especially useful for therapeutic applications. In addition, it is submitted that it could not have been predicted from the literature that the bioactivities of growth factor/cytokine-Ig fusion proteins would vary so significantly depending upon how the growth factor/cytokine is attached to the Ig domain, but given the guidance provided by the inventors, this problem has been addressed for these specific soluble proteins. Therefore, the common structure of the manner of linkage of the growth factor/cytokine to an Ig domain provided by the invention provides the common utility of producing a fusion protein with significant and predictable biological activity of the growth factor/cytokine partner as compared to the native protein. Therefore, the common utility (use as a growth factor/cytokine with improved half-life as compared to the wild-type protein, but with preserved activity of the wild-type protein) is based upon a corresponding common structure that is indeed the basis for this common utility.

Furthermore, a second special technical feature that joins the species within Claim 1 and related claims is the direct joining of a soluble protein (cytokine or growth factor) to an immunoglobulin domain without an intervening peptide linker. It is particularly noted that such a direct fusion is not achieved by changing an amino acid of one of the domains so that the natural amino acid sequence of one or the other domain is interrupted, but rather, the natural sequence of both fusion partners is maintained at the fusion site. The particular advantage of a direct fusion protein is that it is comprised entirely of natural amino acid sequences, which decreases the

possibility that the fusion protein will stimulate an immune response in patients and thereby potentially neutralize or inhibit the therapeutic effects of the fusion protein in the patients.

With regard to the Examiner's comments concerning Gayle et al., Applicants submit that a careful review of the techniques used by Gayle et al. to create the referenced ST2 fusion reveals that these researchers had to modify the natural amino acid sequence of one of the fusion partners in order to fuse the proteins. Therefore, the natural sequence of the fusion partners is not maintained at the fusion site. Specifically, referring to Gayle et al., *J. Biol. Chem.* 271:5784-5789, 1996, a publication by the inventors of the '191 patent that describes the cloning of ST2/IgG-Fc and soluble ST2L/IgG-Fc (copy enclosed), Gayle et al. teach that the ST2 receptor/IgG fusion construct follows procedures of Fanslow et al (*J. Immunology* 149:655-660, 1992) (copy enclosed), which uses a mutated IgG1-Fc domain that contains a substitution of Arg for Lys at position 3 of the IgG-Fc Hinge region. The amino acid sequence of the Hinge region of human IgG1-Fc begins with the sequence: EPKSC. By substituting R (codon of AGA) for K (codon of AAA) in this sequence, Gayle et al. created a Bgl II site (AGATCT) that encompasses the R and S (codon TCT) amino acids. When they amplified the ST2 receptor or soluble ST2 ligand they added a BglII site at the 3' end so they could join this protein to the Fc domain and also cut with BglII. In the process of creating this fusion, they delete the first 2 amino acids of the Hinge region (EP). Also, they must use the mutated Fc domain containing the R substitution. It is not possible to create this fusion if the natural sequences of the Ig domain is used.

In any event, Applicants note that a species requirement is primarily, if not solely, intended to facilitate a search by the Examiner. Applicants note that the Examiner is obligated to examine the generic claims and submits that the scope of the claims of the present invention is not limited to the elected species.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the species election.

Respectfully submitted,

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